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ANDREA Q. RYAN			EXAMINER	
SANOFI-AVENTIS U.S. LLC			DESAL, RITA J	
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BRIDGEWATER, NJ 08807			PAPER NUMBER	
			1625	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary

Application No.

10/691,624

Applicant(s)

BRENDEN ET AL.

Examiner

Rita J. Desai

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 April 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-6 and 23-25 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6, 23-25 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/CDC)
- 4) ☐ Interview Summary (PTO-413)
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____
- Paper No(s)/Mail Date _____

DETAILED ACTION

Claims pending 1 to 6, and 23 to 25 are pending.

The examiner has included $x = 0-4$ in her restriction, with R14 and R15 are a phenyl.

The rejection of the claims 1-6, 23-25 under 35 USC 112 still stands. Applicants arguments are not found to be persuasive.

Even though the scheme 4 on page 26 is given, it is very generic. It does not include all the R14, R15, and various R or the various substituents on the phenyl group.

The claims include several substituents such as

substituents selected from the group consisting of F, Cl, Br, CF₃, OCF₃, CN, COOMe, CONH₂, COMe, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2 or 3 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino,

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- R(3) is $C_yH_zR(16)$;
 y is 0, 1, 2, 3 or 4,
 where y cannot be 0 if R(16) is OR(17) or SO_2Me ;
 R(16) is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, cycloalkyl having 3, 4, 5, 6, 7, 8, 9, 10 or 11 carbon atoms, CF_3 , C_2F_5 , C_3F_7 , CH_2F , CHF_2 , OR(17), SO_2Me , phenyl or naphthyl,
 where phenyl and naphthyl are unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, I, CF_3 , OCF_3 , NO_2 , CN, COOMe, $CONH_2$, COMe, NH_2 , OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;
 R(17) is hydrogen, alkyl having 1, 2, 3, 4 or 5 carbon atoms, cycloalkyl having 3, 4, 5 or 6 carbon atoms, CF_3 or phenyl,
 where phenyl is unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, I, CF_3 , OCF_3 , NO_2 , CN, COOMe, $CONH_2$, COMe, NH_2 , OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

R12 is again R9,

Then these are further substituted.

The examples given in the specifications have very few substituents .

The scope is so broad and the examples provided are very few, considering the unpredictability of the pharmaceutical art.

The scheme does not show all the starting materials. As per MPEP 2164.01 (b):

A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to make the invention are available. In the biotechnical area, this is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after extensive screening. The Court in *In re Ghiron*, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. The same can be said if certain chemicals are

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required to make a compound or practice a chemical process. In re Howarth, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981).

Only a few substituents are shown, as given in the rejection.

If one were to look at the data for 14a-14f compounds in the table on page 96,97 (14c data is missing), it can be seen that that activity varies so much 3.2 to .4 even with a single alkyl substitution..

Applicants claims have so variables and large groups that the full scope is not enabled.

Thus the rejection still stands.

The rejection is being repeated here.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1

) R5-R8 to be H does not reasonably provide enablement for all the other various substituents..

2) for the CF3 and halogen as the substituents on phenyl does not enable all the other various substituent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

In applicant's arguments in paper #9, only two of the guidelines for making a determination of whether or not the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" have been used.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

1) The breadth of the claims: The instant claims encompass many compounds from an aromatic carbocyclic moiety to an aromatic carbocyclic moiety having many large electron withdrawing and bulky groups substituted on it. These compounds cover a very wide range of compounds.

2) The nature of the invention: The invention is a (highly) substituted biphenyl compound that has pharmaceutical use.

3) The state of the prior art: The state of the prior art is that the drugs and the enzymes react in a lock and key mechanism and the structure of the compound has to be specific. Even a difference of a methyl group versus a hydrogen changes the properties altogether. A good example is a theophylline versus caffeine. They differ by just a methyl group but one of them has a pharmaceutical use as a bronchodilator. There is no absolute predictability and no established correlation between the different substitutions on a core that they would all behave in the exact same way. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

Also as given in the preface below it is not easy to make the various compounds. As stated in the preface to a recent treatise:

"Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry

textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such workChemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious) " Dorwald F. A.

Side Reactions in Organic Synthesis, 2005, Wiley: VCH, Weinheim pg. IX of Preface.

4) The level of one of ordinary skill: The ordinary artisan is highly skilled.

5) The level of predictability in the art: It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In *re Fisher*, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. The level of unpredictability in the art is very high. The compounds which differ by a methyl group also show different properties, for e.g. theophylline and caffeine. One of them is a bronchodilator and they differ only by a methyl group.

In *re Fisher* 166 USPQ 18 states:-

It is apparent that such an inventor should be allowed to dominate the future patentable inventions of others where those inventions were based in some way on his teachings. Such improvements, while unobvious from his teachings, are still within his contribution, since the improvement was made possible by his work. It is equally apparent, however, that he must not be permitted to achieve this dominance by claims which are insufficiently supported and hence not in compliance with the first paragraph of 35 U.S.C. 112. That paragraph requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by

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the specification to persons of ordinary skill in the art. In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

6) The amount of direction provided by the inventor: The inventor provides very little direction in the instant specification. There are no examples with the R's being the various substituents as given in the claims

7) The existence of working examples: The instant specification does not have any working examples and there is not data provided for compounds with the various substituents.

8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: Since there are no working examples, the amount of experimentation is very high and burdensome. And in view of the state of the art and the predictability in the art it cannot be seen how these compounds can be made and used commensurate to the scope of the compounds.

Taking the above eight factors into consideration, it is not seen where the instant specification enables the ordinary artisan to make and/or use the instantly claimed invention.

Genetech Inc Vs Nova Nordisk 42 USPQ 2d 1001.

"A patent is not a hunting license. It is not a reward for search but compensation for its successful conclusion and patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that,

based on the evidence regarding each of the above factors, the specification, at the

time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

Conclusion

Claims 1-6, 23-25 stand rejected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rita J. Desai whose telephone number is 571-272-0684. The examiner can normally be reached on Monday - Friday, flex time..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Rita J. Desai
Primary Examiner
Art Unit 1625

R.D.
July 11, 2008

/Rita J. Desai/
Primary Examiner, Art Unit 1625